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Risks of Infection and Mortality Among Patients Colonized With *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Validation of Scores and Proposal for Management

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Background. The management and indication of empiric treatment in *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* (KPC-Kp)–colonized patients should be improved.

Methods. A prospective cohort of 94 patients colonized by KPC-Kp was followed for 90 days to validate (i) the Giannella risk score (GRS) to predict the development of any type of KPC-Kp infection and (ii) the INCREMENT-CPE score (ICS) to predict 30-day mortality in patients with infection. Both scores were combined to recommend appropriate empiric treatment. The predictive ability of the scores was measured by calculating the area under the receiver operating characteristic (AUROC) curve.

Results. The GRS showed an AUROC curve for infection due to KPC-Kp of 0.92 (95% confidence interval [CI], .87–.98). The optimal cutoff point was fixed at <7 and ≥7 (92.9% sensitivity, 84.8% specificity); infection developed in 6.3% patients in the 0–6 GRS group and in 84.8% patient in the ≥7 GRS group. According to the ICS, the severity of the infection was also significantly higher in the ≥7 GRS group. The ICS showed an AUROC of 0.78 (95% CI, .65–.91) for 30-day all-cause mortality among patients with infection. A classification and regression tree analysis confirmed the GRS cutoff point at 7, and selected ≥12 points to predict a KPC-Kp infection with a high ICS.

Conclusions. Our results validate the GRS and ICS for indicating empiric therapy in KPC-Kp–colonized patients.

Keywords. KPC; carbapenemase-producing *Klebsiella pneumoniae*; colonization; risk scores; management.

The high mortality of infections caused by *Klebsiella pneumoniae* carbapenemase (KPC)–producing *K. pneumoniae* (KPC-Kp) requires control measures to reduce its dissemination, as well as objective criteria to improve the indication of appropriate empiric treatment in infected patients. The risk of developing an active infection in colonized patients is controversial, especially regarding severe infections such as bacteremia. Empiric treatment is frequently inadequate, and adequate treatment is initiated after the susceptibility test is available [1–3]. This delay in initiating appropriate treatment may have a negative impact on mortality. Giannella et al [4] developed a bacteremia risk score that is applicable to colonized patients (Giannella risk score [GRS]), while Gutiérrez-Gutiérrez et al [1] developed a mortality risk score (INCREMENT-CPE score [ICS]) in patients with bacteremia to determine the best treatment option (monotherapy vs combination therapy) [5]. Although this tool can aid in providing patients the best care, it needs an external validation.

Our objectives were (i) to validate the GRS in our cohort of KPC-Kp–colonized patients (ANGEL cohort) as a predictor not only of bacteremia but also of other active KPC-Kp infections; (ii) to validate the ICS in a subcohort of patients with any type of KPC-Kp infection as a predictor of mortality; and (iii) to study the utility of combining both scores to recommend appropriate empiric treatment.

MATERIALS AND METHODS

Study Design

The GRS was validated in a prospective observational cohort including all adult patients (≥18 years of age) with rectal colonization by KPC-Kp detected at the Hospital Universitario Reina Sofía, a 1000-bed tertiary center in Cordoba, Spain. The study was carried out from July 2012 to November 2015 during

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a protracted outbreak of infections due to clonal KPC-Kp. Patients colonized by KPC-Kp were detected by means of rectal swab culture, which was performed among all patients admitted to the intensive care or hematology units, and hospitalized patients undergoing abdominal interventions and transplantation previously admitted to units affected by the outbreak. Colonized patients were also studied for additional sites of colonization including urine, respiratory tract, and chronic ulcers. Patients receiving intestinal decontamination with oral, nonabsorbable antibiotics were excluded. All included patients were followed as indicated by the clinical protocols of the hospital. For the analysis, the follow-up was censored at 90 days, at event (infection by KPC-Kp), or at death. Patients with an initial negative rectal swab underwent at least a second rectal swab during follow-up. Patients from the previous cohort with a KPC-Kp infection were included in the subcohort formed to validate the ICS.

The study was approved by the Ethics Committee of the Hospital Universitario Reina Sofía-IMIBIC (code BACANG-2017-04). All the data collected were anonymized.

Outcome Variables and Population for Each Objective

For the validation of the GRS, the main outcome variable was the development of at least 1 episode of KPC-Kp infection (including bacteremia) during the 90 days of follow-up. For the validation of the ICS, the main outcome variable was 30-day all-cause mortality measured from the day on which the cultures to diagnose the infection were taken.

Data were collected retrospectively using a standardized form. The explanatory variables for the validation of the GRS were studied at the time of rectal colonization, and the explanatory variables for the validation of the ICS were studied on the day the culture to diagnose the infection was taken. The variables included age, sex, ward of admission, solid organ transplantation, chronic kidney disease, neutropenia, and immunosuppression. Variables regarding the treatment received (appropriate empiric therapy, time from culture to appropriate therapy, and appropriate monotherapy or combination) in patients who developed a KPC-Kp infection were also collected. The variables included in the GRS were admission to the intensive care unit (2 points), invasive abdominal procedures (3 points), chemotherapy/radiation therapy (4 points), and colonization at site besides rectal (5 points per each additional site) [4]. The variables included in the ICS were severe sepsis or septic shock at presentation (5 points), Pitt bacteremia score ≥6 (4 points), Charlson index ≥2 (3 points), and source of bloodstream infection other than urinary or biliary tracts (3 points; because we included patients with nonbacteremic infections, the site of infection was applied) [1]. Receiving early targeted therapy [1] was not considered to validate as we were assessing pretreatment risk of mortality. Patients with ≥8 and <8 points in the ICS were considered to be at high and low risk of mortality, respectively [5].

Definitions

Patients with rectal colonization due to KPC-Kp were defined as patients with KPC-Kp isolation in a rectal swab in the absence of infection. The day of culture was taken as the starting date of the follow-up. All infections were microbiologically proven and were defined following the Centers for Disease Control and Prevention criteria [6]. Bacteremia was defined as the isolation of KPC-Kp in the blood culture with systemic inflammatory response. The date of extraction of the index culture was considered the date of infection.

Microbiological Studies

Rectal swabs were inoculated on a selective chromogenic agar plate (bioMérieux). Blood cultures were performed using the BACTEC 9240 automatic blood culture detection system (Becton Dickinson). The remaining samples were processed using standard microbiological techniques. Antibiotic susceptibility tests were performed using the gram-negative REV.2 WIDER panel (Siemens Healthcare Diagnostics) or gradient strips when needed (Liofilmchem).

The KPC-Kp index isolates in this outbreak were previously characterized as producing KPC-3 and belonging to the ST512 clone (reference laboratory of the Vírgen Macarena University Hospital of Seville, Spain). The characteristics of the strain have been previously reported [7].

Statistical Analysis

The results were expressed as the median and interquartile range (IQR) for the continuous variables and as percentages for the categorical variables. The continuous variables were compared using the Kruskal-Wallis test, the Student *t* test, or the Mann-Whitney *U* test. The categorical variables were compared using the χ^2 test or Fisher exact test as appropriate. The area under the receiver operating characteristic (AUROC) curve with a 95% confidence interval (CI) was used to quantify the discriminative capacity of the GRS to predict KPC-Kp infection/bacteremia. Sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for different cutoff points of this score to obtain the optimal cutoff points. Additionally, classification and regression tree (CART) analysis was performed to confirm these optimal cutoff points. Multivariate logistic regression analyses were also performed to assess the independent association of GRS with development of a KPC-Kp infection and mortality at day 30. The Akaike information criterion was used to select the final logistic models. SPSS version 20.0 software, R software (version 3.0.1), and CART software 8.0 (Salford Systems) were used for the analysis.

RESULTS

During the study period, rectal colonization was studied in 903 patients, among whom 94 KPC-Kp–colonized patients were identified. Of the colonized patients, 35 were female (37.2%),

the median age was 63 years (IQR, 53–72.5 years), 42 (44.7%) developed a KPC-Kp infection (22 were bacteremic), 34 (36.2%) developed an infection due to a non–KPC-Kp microorganism (7 were bacteremic), and 18 (19.1%) did not develop any type of infection. The characteristics of the patients are shown in Table 1. Significant differences were observed among groups regarding age, surgery in the previous 3 months, median GRS, ward of admission, solid organ transplantation, and mortality. Among patients with infection, significant differences were observed in the frequency of bacteremia (52.4% vs 20.6%, $P < .001$) between the KPC-Kp and non–KPC-Kp infection groups, respectively.

Validation of the Giannella Risk Score to Predict *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* Infection: Optimal Cutoff Point of Risk

GRS showed a linear association with infection rates; these were 3.8%, 30%, 76%, and 100% for GRS values 0–3, 4–7, 8–12, and 15–20, respectively. The application of the GRS in the cohort of 94 colonized patients showed an AUROC for KPC-Kp infection of 0.92 (95% CI, .87–.98). The optimal cutoff point was set at <7 and ≥7 (Supplementary Figure 1). The proportion of patients, sensitivity, specificity, PPV, NPV, and accuracy values for different breakpoints of the score values are listed in Table 2. The <7 and ≥7 cutoff showed a 92.9% sensitivity; only 3 of 48 cases with a GRS <7 developed a KPC-Kp infection and 1 died (not attributable to infection). The specificity was 84.8% (39 of 46 cases with a GRS ≥7 developed a KPC-Kp infection), and the highest accuracy was 89.4%. Values of the score ≥15 showed a specificity of 100%.

To further test the predictive ability of GRS when considering other variables, a CART analysis was performed in the cohort of 94 colonized patients. The covariates considered were age, sex, ward of admission, Charlson index [8], McCabe classification [9], neutropenia, and immunosuppression; however, the final model obtained (Supplementary Figure 2) only selected GRS as the best predictor of KPC-Kp infection. The optimal cutoff of the GRS at <7 and ≥7 was also selected by CART as the best first splitter. A second cutoff at <15 and ≥15 was selected for patients with a GRS ≥7, thus confirming the results previously obtained (Table 2).

Table 3 shows the characteristics of the patients according to the first optimal cutoff point obtained (GRS <7 and ≥7). Importantly, among the 48 patients with <7 points, 29 (60.4%) developed a non–KPC-Kp infection, 16 (33.3%) had no infection, and only 3 (6.3%) developed a KPC-Kp infection. On the other hand, among the 46 patients with ≥7 points, 39 (84.8%) developed a KPC-Kp infection (21 were bacteremic), 5 (10.9%) developed a non–KPC-Kp infection, and only 2 cases (4.3%) did not develop infection. Additionally, there were significant differences in the distribution of the following variables between the 2 groups: age, surgery in the previous 3 months,

Table 1. Characteristics of 94 Patients Colonized With *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Characteristic	No Infection (n = 18)	Non–KPC-Kp Infection (n = 34)	KPC-Kp Infection (n = 42)	*P* Value
Age, y, median (IQR)	77.5 (69–84.7)	62.0 (53–69.7)	59.0 (47–67)	<.001[a]
Male sex	7 (38.9)	14 (41.2)	14 (33.3)	.77
Surgery in the previous 3 months	4 (8.2)	17 (34.8)	28 (57.1)	.006
Antimicrobial therapy in the previous month (for ≥2 d)	14 (77.8)	26 (76.5)	31 (73.8)	.94
Ward of admission before infection				<.001
Medical	13 (72.2)	10 (29.4)	7 (16.7)	
Surgical	4 (22.2)	10 (29.4)	9 (21.4)	
Intensive care unit	1 (5.6)	14 (41.2)	26 (61.9)	
Neutropenia	2 (11.1)	4 (11.8)	11 (26.2)	.19
Giannella risk score, median (IQR)	3.5 (0–5)	5.0 (2–5)	12 (10–15)	<.001[a]
Chronic kidney disease	5 (27.8)	7 (20.6)	9 (21.4)	.82
Solid organ transplantation	1 (5.6)	9 (26.5)	4 (9.5)	.05
Charlson comorbidity index, median (IQR)	4 (3–5)	4 (2.25–6)	2.5 (1–4)	.12[a]
Immunosuppression	9 (50.0)	16 (47.1)	24 (57.1)	.67
Bacteremia	…	7 (20.6)	22 (52.4)	<.001
Source of infection				.39
Pneumonia	…	16 (47.1)	22 (52.4)	
Intra-abdominal	…	4 (11.8)	8 (19.0)	
Catheter		4 (11.8)	6 (14.3)	
Urinary		5 (14.7)	5 (11.9)	
Skin and skin structures		3 (8.8)	0	
Surgical wound		2 (5.8)	1 (2.4)	
Died during follow-up	4 (22.2)	9 (26.5)	24 (57.1)	.006

Data are presented as No. of patients (percentage) except where specified. *P* values were calculated by the χ^2 test, except where otherwise specified.

Abbreviations: IQR, interquartile range; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*.

[a]Kruskal-Wallis test.

Table 2. Proportion of Patients, True Positives, False Positives, True Negatives, False Negatives, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy for Different Breakpoints for Developing a *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* Infection According to Giannella Score

Colonized Patients (N = 94)	Proportion of Patients (%)	TP (No.)	FP (No.)	TN (No.)	FN (No.)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Score ≥0	100	42	52	0	0	100	0	44.7	…	44.7
Score ≥2	88.30	42	41	11	0	100	21.2	50.6	100	56.4
Score ≥3	75.53	41	30	22	1	97.6	42.3	57.7	95.7	67.0
Score ≥4	72.34	41	27	25	1	97.6	48.1	60.3	96.2	70.2
Score ≥5	71.28	41	26	26	1	97.6	50.0	61.2	96.3	71.3
Score ≥7	48.94	39	7	45	3	92.9	86.5	84.8	93.8	89.4
Score ≥8	40.43	32	6	46	10	76.2	88.5	84.2	82.1	83.0
Score ≥10	39.36	32	5	47	10	76.2	90.4	86.5	82.5	84.0
Score ≥12	26.60	22	3	49	20	52.4	94.2	88.0	71.0	75.5
Score ≥15	13.83	13	0	52	29	31.0	100	100	64.2	69.1
Score ≥17	8.51	8	0	52	34	19.0	100	100	60.5	63.8
Score ≥20	4.26	4	0	52	38	9.5	100	100	57.8	59.6
Score ≥21	0	0	0	52	42	0	100	…	55.3	55.3

Abbreviations: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

Table 3. Characteristics of 94 Patients Colonized With *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* in the Giannella Score <7 and ≥7 Groups

Characteristic	GRS 0–6 (n = 48)	GRS ≥7 (n = 46)	*P* Value
Age, y, median (IQR)	66.5 (56.5–76.2)	60 (49.0–67.0)	.007[a]
Male sex	16 (33.3)	19 (41.3)	.42
Surgery in the previous 3 mo	17 (35.4)	32 (69.6)	<.001
Antimicrobial therapy in the previous month (for ≥2 d)	36 (75.0)	35 (76.1)	.90
Clinical unit before infection			<.001
Medical	24 (50.0)	6 (13.0)	
Surgical	11 (22.9)	12 (26.1)	
Intensive care unit	13 (27.1)	28 (60.9)	
Neutropenia	6 (12.5)	11 (23.9)	.15
Chronic kidney disease	13 (27.1)	8 (17.4)	.26
Solid organ transplantation	10 (20.8)	4 (8.7)	.10
Charlson comorbidity index, median (IQR)	4 (3–6)	2.5 (1–4)	.01[a]
Immunosuppression	26 (54.2)	23 (50.0)	.69
No infection	16 (33.3)	2 (4.3)	<.001
Non–KPC-Kp infection	29 (60.4)	5 (10.9)	<.001
KPC-Kp infection	3 (6.2)	39 (84.8)	<.001
Non–KPC-Kp bacteremia	4 (8.3)	3 (6.5)	.74[b]
KPC-Kp bacteremia	1 (2.1)	21 (45.7)	<.001
ICS, median (IQR)[c]	3 (3–3)	10 (6–11)	<.001[a]
High risk of mortality according to ICS	1 (2.1)	27 (58.7)	<.001[a]
Died during follow-up	13 (27.1)	24 (52.2)	.01

Data are presented as No. of patients (%) except where specified. *P* values were calculated by the χ^2 test, except where otherwise specified.

Abbreviations: GRS, Giannella risk score; ICS, INCREMENT-CPE score; IQR, interquartile range; KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*.

[a]Mann-Whitney *U* test.

[b]Fisher exact test.

[c]Median and IQR of the ICS were calculated only in patients with a KPC-Kp infection in each group.

ward of admission, Charlson index, and severity of infection according to ICS. Mortality was also different. A multivariate logistic regression analysis confirmed the independent association between GRS and the risk of KPC-Kp infection (adjusted odds ratio [OR] per unit, 1.68 [95% CI, 1.40–2.12]; $P < .0001$; Supplementary Table 1).

Validation of the INCREMENT-CPE to Predict 30-Day All-Cause Mortality

The application of the ICS in the subcohort of 42 colonized patients who developed a KPC-Kp infection showed an AUROC for 30-day all-cause mortality of 0.78 (95% CI, .65–.91). Similar results were obtained when the ICS was calculated including the variable receiving empiric therapy and inappropriate early targeted therapy (AUROC, 0.79 [95% CI, .66–.93]). All but 3 (who died before culture was available) received an appropriate therapy within the 5 days from the culture. Overall, 16 and 26 patients in this subcohort had <8 (low risk for mortality) and ≥8 (high risk) points in ICS, respectively. Mortality was 21.3% (5 patients) in the low-risk group and 73.1% (19 patients) in the high-risk group ($P = .008$). The logistic regression multivariate model obtained confirmed the significant association between ICS and mortality at day 30 in the subcohort (adjusted OR per unit, 1.33 [95% CI, 1.10–1.69]; $P = .008$; Supplementary Table 2).

Combining the Predictive Ability of Giannella Risk Score and INCREMENT-CPE and the Development of a Management Algorithm for *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*–Colonized Patients

To investigate whether a GRS value might predict not only patients who will develop or not an infection due to KPC-Kp, but also patients in whom the infection would be associated with a high risk of mortality (and therefore, in whom preventive

measures might be more efficient), a second CART analysis was performed. In this analysis, among patients with a GRS score >6 (therefore, at high risk of KPC-Kp infection), a GRS score ≥12 points was predictive of a high ICS. Thus, the proportion of patients who developed a KPC-Kp infection with high ICS was 38.1% (8/31) among those with a GRS 7–11, and 72% (18/25) among those with a GRS ≥12 (Supplementary Figure 3).

Supplementary Figure 4 shows the flowchart of the KPC-Kp infections in the cohort of 94 colonized patients according to the established cutoff points for the GRS and ICS. Based on this flowchart and on the results obtained, a management algorithm of patients colonized with KPC-Kp is proposed (Figure 1).

DISCUSSION

To the best of our knowledge, our study provides the first external validation of both the GRS [4] and the ICS [1]. The GRS was applied to a selected group of KPC-Kp–colonized patients and showed very good predictive ability for the development of not only bacteremia (for which the score was developed) but also any type of KPC-Kp infection. The ICS was applied to colonized patients who developed a KPC-Kp infection (and again, not only bacteremia, for which the score was developed) and showed a good predictive ability for mortality.

The worldwide spread of KPC-Kp and other carbapenem-resistant Enterobacteriaceae has been associated with clonal outbreaks, for which very high mortality rates are frequently reported [10, 11]. This was also observed in our cohort; infections due to KPC-Kp were mostly severe in this selected population, with a high frequency of bacteremia (Table 1). Interestingly, the median ICS (which predicts the risk of mortality) in patients with KPC-Kp infections compared to those infected by other microorganisms was significantly higher as was mortality. In this scenario, it is necessary to establish objective criteria to aid physicians in deciding which patients should rapidly start empiric treatment active against the outbreak bacteria to reduce mortality. This is far from easy because the susceptibility profile of these bacteria may force physicians to use newer drugs (eg, ceftazidime-avibactam), which may need to be used prudently and reserved for specific situations or combinations of a broad-spectrum agent (eg, carbapenems) with a "second line" drug, some of which are associated with high toxicity (ie, gentamicin, colistin) or of doubtful effectiveness (ie, tigecycline) [12–14]. In the case of extensively drug-resistant isolates showing high-level resistance to both colistin and carbapenems (such as the isolate causing the outbreak in this study), constructing an empiric regimen is even more difficult [15]. Therefore, when faced with KPC-Kp–colonized patients who develop symptoms of infection, deciding about empiric treatment is highly challenging, as a regimen with only a second-line drug might be less efficacious than other drugs for susceptible organisms but would be needed if the KPC-Kp is causing the infection.

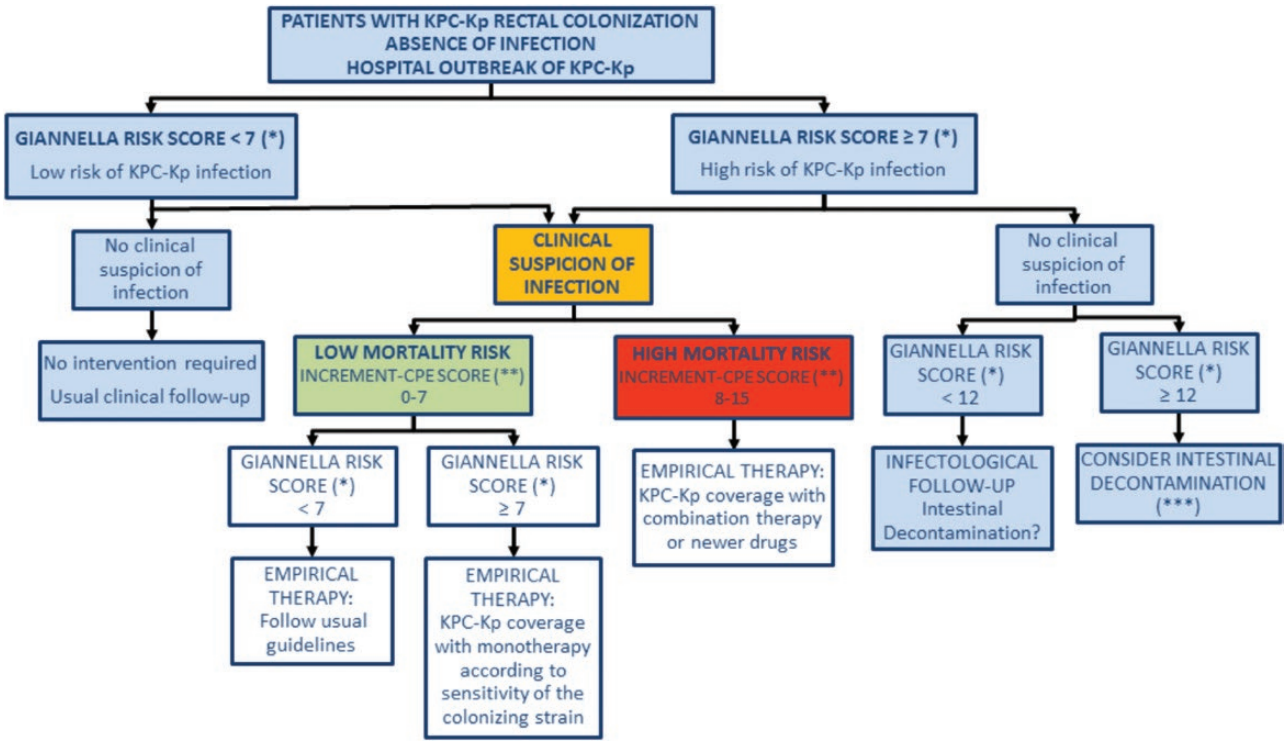

Figure 1. Management algorithm for patients colonized with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* (KPC-Kp). *[4]; **[1]; ***[16].

Standardization of clinical practice is improved if decisions can be based on objective criteria. In this sense, the development of the GRS [4] proved to be a valuable tool to classify the risk of infection in colonized patients. However, objective criteria are needed to guide the appropriate empiric treatment when an infection is suspected in a colonized patient. This study shows that it is possible to propose a management algorithm based on the combined use of the GRS and the ICS (Figure 1). The cutoff point of the GRS that best discriminates the risk of KPC-Kp infection was set at 7 points. In our opinion, colonized patients at low risk (GRS <7) should have the usual follow-up of their underlying disease. In contrast, patients at high risk of developing a KPC-Kp infection (GRS ≥7) must have a different management, since we have previously shown that the use of selective intestinal decontamination reduces the risk of mortality in a selected group of colonized patients [16]. Based on our data, we proposed that intestinal decontamination should be considered in patients with a GRS ≥12, which predicted the development of a KPC-Kp infection with high mortality; however, more studies are needed, particularly in patients with high GRS score and multisite colonization. Patients with a GRS of 7–12 points should have individualized management. The indication of decontamination should be made by carefully assessing the risks and benefits of each case.

When a colonized patient develops an infection, the scenario is completely different. Our results demonstrate that the application of the ICS at this time may help to decide which empiric treatment should be used. If the patient is at high risk of mortality (ICS 8–15), there is no doubt that the empiric treatment should cover KPC-Kp with at least 2 active drugs (according to the antibiogram of the colonizing strain). If the patient is at low risk of mortality (ICS 0–7), we recommend indicating KPC-Kp coverage with monotherapy only to patients with a GRS ≥7. In the rest of patients, the empiric treatment should follow the usual guidelines, and coverage of the colonizing strain is not needed.

The main difference between our cohort and that of Giannella et al [4] and others [17, 18] is the proportion of colonized patients who developed infection. In our cohort, 44.7% of patients developed a KPC-Kp infection (bacteremia in 23.4%). These extraordinarily high figures are explained by the fact that the patients included in our study had a high baseline risk of developing any infection. However, we cannot rule out that the high rate of infection might be due to a specific virulence of the KPC-producing strain.

Our study has important limitations. It is a single-center study with a limited sample size depending on the available cases. Nevertheless, our results allow us to validate the clinical utility of the GRS [4] and ICS [1] to indicate empiric therapy in colonized patients. Patients were colonized by a KPC-producing epidemic strain and most of them belonged to specific populations, and the results might not be applicable to other situations. However, in the absence of larger studies, our results allow us to establish a management algorithm that can be very useful for making objective decisions. There is no doubt that our results should be validated in larger cohorts and interventional studies. Of course, these results would only be applicable to patients selected with the criteria used in this study.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al; Investigators from the REIPI/ESGBIS/INCREMENT Group. A predictive model of mortality in patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae. Mayo Clin Proc **2016**; 91:1362–71.
2. Castón JJ, Lacort-Peralta I, Martín-Dávila P, et al. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients. Int J Infect Dis **2017**; 59:118–23.
3. Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F, et al. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*. J Antimicrob Chemother **2015**; 70:905–13.
4. Giannella M, Trecarichi EM, De Rosa FG, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect **2014**; 20:1357–62.
5. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al; REIPI/ESGBIS/INCREMENT Investigators. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis **2017**; 17:726–34.
6. Centers for Disease Control and Prevention Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. Morb Mortal Wkly Rep **2009**; 58:256–60.
7. López-Cerero L, Egea P, Gracia-Ahufinger I, et al. Characterisation of the first ongoing outbreak due to KPC-3-producing *Klebsiella pneumoniae* (ST512) in Spain. Int J Antimicrob Agents **2014**; 44:538–40.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
9. McCabe WR, Jackson GG. Gram-negative bacteremia: II. Clinical, laboratory and therapeutic observations. Arch Intern Med **1962**; 110:856–64.

10. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev **2012**; 25:682–707.
11. Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. Clin Microbiol Infect **2012**; 18:54–60.
12. Michail G, Labrou M, Pitiriga V, et al. Activity of tigecycline in combination with colistin, meropenem, rifampin, or gentamicin against KPC-producing Enterobacteriaceae in a murine thigh infection model. Antimicrob Agents Chemother **2013**; 57:6028–33.
13. Hodiamont CJ, Juffermans NP, Bouman CS, de Jong MD, Mathôt RA, van Hest RM. Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis. Int J Antimicrob Agents **2017**; 49:204–11.
14. Perez F, El Chakhtoura NG, Papp-Wallace KM, Wilson BM, Bonomo RA. Treatment options for infections caused by carbapenem-resistant Enterobacteriaceae: can we apply "precision medicine" to antimicrobial chemotherapy? Expert Opin Pharmacother **2016**; 17:761–81.
15. Machuca I, Gutiérrez-Gutiérrez B, Gracia-Ahufinger I, et al. Mortality associated with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance: importance of combination therapy without colistin and carbapenems. Antimicrob Agents Chemother **2017**; 61. doi:10.1128/AAC.00406-17.
16. Machuca I, Gutiérrez-Gutiérrez B, Pérez Cortés S, et al. Oral decontamination with aminoglycosides is associated with lower risk of mortality and infections in high-risk patients colonized with colistin-resistant, KPC-producing *Klebsiella pneumoniae*. J Antimicrob Chemother **2016**; 71:3242–9.
17. Borer A, Saidel-Odes L, Eskira S, et al. Risk factors for developing clinical infection with carbapenem-resistant *Klebsiella pneumoniae* in hospital patients initially only colonized with carbapenem-resistant *K pneumoniae*. Am J Infect Control **2012**; 40:421–5.
18. Schechner V, Kotlovsky T, Kazma M, et al. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? Clin Microbiol Infect **2013**; 19:451–6.